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Published in:
Critical reviews in clinical laboratory sciences

DOI:
[10.1080/10408363.2018.1460576](https://doi.org/10.1080/10408363.2018.1460576)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2018

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Piek, A., Du, W., de Boer, R. A., & Silljé, H. H. W. (2018). Novel heart failure biomarkers why do we fail to exploit their potential? *Critical reviews in clinical laboratory sciences*, 55(4), 246-263.
<https://doi.org/10.1080/10408363.2018.1460576>

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To cite this article: Arnold Piek, Weijie Du, Rudolf A. de Boer & Herman H. W. Silljé (2018) Novel heart failure biomarkers: why do we fail to exploit their potential?, Critical Reviews in Clinical Laboratory Sciences, 55:4, 246-263, DOI: [10.1080/10408363.2018.1460576](https://doi.org/10.1080/10408363.2018.1460576)

To link to this article: <https://doi.org/10.1080/10408363.2018.1460576>



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Published online: 17 Apr 2018.



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REVIEW ARTICLE



Novel heart failure biomarkers: why do we fail to exploit their potential?

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ABSTRACT

Plasma biomarkers are useful tools in the diagnosis and prognosis of heart failure (HF). In the last decade, numerous studies have aimed to identify novel HF biomarkers that would provide superior and/or additional diagnostic, prognostic, or stratification utility. Although numerous biomarkers have been identified, their implementation in clinical practice has so far remained largely unsuccessful. Whereas cardiac-specific biomarkers, including natriuretic peptides (ANP and BNP) and high sensitivity troponins (hsTn), are widely used in clinical practice, other biomarkers have not yet proven their utility. Galectin-3 (Gal-3) and soluble suppression of tumorigenicity 2 (sST2) are the only novel HF biomarkers that are included in the ACC/AHA HF guidelines, but their clinical utility still needs to be demonstrated. In this review, we will describe natriuretic peptides, hsTn, and novel HF biomarkers, including Gal-3, sST2, human epididymis protein 4 (HE4), insulin-like growth factor-binding protein 7 (IGFBP-7), heart fatty acid-binding protein (H-FABP), soluble CD146 (sCD146), interleukin-6 (IL-6), growth differentiation factor 15 (GDF-15), procalcitonin (PCT), adrenomedullin (ADM), microRNAs (miRNAs), and metabolites like 5-oxoproline. We will discuss the biology of these HF biomarkers and conclude that most of them are markers of general pathological processes like fibrosis, cell death, and inflammation, and are not cardiac- or HF-specific. These characteristics explain to a large degree why it has been difficult to relate these biomarkers to a single disease. We propose that, in addition to clinical investigations, it will be pivotal to perform comprehensive preclinical biomarker investigations in animal models of HF in order to fully reveal the potential of these novel HF biomarkers.

Abbreviations: ACC: American College of Cardiology; ACE: angiotensin-converting enzyme; ADM: adrenomedullin; AHA: American Heart Association; ANP: atrial-type natriuretic peptide; ARB: angiotensin receptor blocker; BACH: Biomarkers in Acute Heart Failure; bio-ADM: bioactive amidated ADM; BNP: B-type natriuretic peptide; CAP: community acquired pneumonia; CD146: cluster of differentiation 146, also known as the melanoma cell adhesion molecule (MCAM) or cell surface glycoprotein MUC18; CD146-L: long CD146 isoform; CGRP: calcitonin gene-related peptide; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; ESC: European Society of Cardiology; Gal-3: galectin-3; GDF-15: growth differentiation factor 15; GH: growth hormone; HE4: human epididymis protein 4; HF: heart failure; H-FABP: heart fatty acid-binding protein; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; hsTn: high sensitivity cardiac troponin; IGF-1: insulin-like growth factor 1; IGFBP-7: insulin like growth factor-binding protein 7; IL-6: interleukin-6; LV: left ventricle; LVAD: left ventricular assist device; miRNA: microRNA; MR-proADM: mid-regional pro-ADM; MR-proANP: mid-regional pro-ANP; NT-proANP: N-terminal prohormone of ANP; NT-proBNP: N-terminal prohormone of BNP; OPLAH: 5-oxoprolinase, ATP-hydrolyzing; PCT: procalcitonin; PKG: protein kinase G; sCD146: soluble CD146; sST2: soluble ST2; ST2: suppression of tumorigenicity 2; TIMP-2: tissue inhibitor of metalloproteinase 2; TMAO: trimethylamine N-oxide; TNF-R 1 α : tumor necrosis factor alpha receptor 1; WFDC2: whey acidic protein four-disulfide core domain 2, WAP-4C

ARTICLE HISTORY

Received 20 November 2017

Revised 8 March 2018

Accepted 30 March 2018

Published online 14 April 2018

KEYWORDS

Biomarkers; heart failure; fibrosis; inflammation; cell death

Heart failure: a complex syndrome

Heart failure (HF) is a complex syndrome that is characterized by reduced cardiac function and results in insufficient cardiac output to meet peripheral tissue

metabolic demands [1,2]. It is prevalent in Western society, with more than 8% of the population aged 75 and older being diagnosed with HF [1,3,4]. Reduced cardiac output leads to the accumulation of fluid in lungs and

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other tissues, resulting in breathlessness, peripheral edema, and fatigue [1]. Thus, HF is not limited to cardiac dysfunction but also affects extra-cardiac organs and tissues. Due to different etiologies and underlying pathophysiological processes, HF is a heterogeneous disease, and plasma biomarkers could potentially contribute to the improvement of patient stratification and to guide therapy. In clinical association studies, many potential HF biomarkers have been identified and investigated for their diagnostic and prognostic values. Despite these efforts, limited progress has been made in introducing these novel biomarkers into daily clinical practice. Because HF can affect multiple organs, and these novel biomarkers are not exclusively expressed in the heart, it is difficult to draw conclusions from their plasma levels and to directly associate the levels with specific indices of cardiac remodeling and function. This issue needs to be clarified, and most likely it will require preclinical investigations in animal models of HF in addition to clinical studies. Numerous excellent reviews that discuss HF biomarkers have been published [5–8], and this review is not meant to provide a complete overview of novel HF markers. Instead, we will briefly describe some novel (and established) HF biomarkers, and discuss them particularly in light of their (non-) cardiac nature and potential involvement in other diseases and conditions. We will outline challenges and pitfalls that we face and discuss why research should focus not only on clinical studies but also on preclinical studies using animal models.

Heart failure pathology

HF is the end-stage syndrome of most cardiovascular diseases, including myocardial infarction, hypertension, aortic stenosis, valve insufficiencies, and arrhythmias [1,3,9]. These diseases increase cardiac stress; to cope with this stress and to maintain cardiac function, morphological, structural, and functional alterations occur in the heart, a process termed cardiac remodeling [10]. Excessive extracellular matrix production (fibrosis) by fibroblasts and myofibroblasts, cardiomyocyte growth (hypertrophy), and infiltration of immune cells and elevated inflammation are the main processes that underlie cardiac remodeling [11–14]. Initially, these processes are beneficial and can be considered compensatory mechanisms, but with sustained cardiac stress, remodeling mechanisms eventually become pathological and reduce cardiac function [10–14]. Ongoing cardiac fibrosis results in stiffening of the cardiac muscular wall, which affects cardiac relaxation and contraction, may limit oxygen and nutrient diffusion and can disturb cardiac electrophysiology and induce rhythm disturbances [11]. Pathological cardiomyocyte hypertrophy limits cardiac function through alterations in Ca^{2+} handling,

changes in excitation–contraction coupling, sarcomere dysfunction, increased oxidative stress, and metabolic and energetic remodeling [11–14]. A vicious cycle is set up in which further deterioration of cardiac function stimulates further remodeling, which eventually may result in decompensated HF [11,15].

Different etiologies of HF result in different types of remodeling. For instance, myocardial infarction activates inflammatory pathways, stimulates replacement fibrosis and may drive eccentric hypertrophy, resulting in HF with reduced ejection fraction (HFrEF). Hypertension, on the other hand, may drive concentric hypertrophy and interstitial fibrosis, resulting in HF with preserved ejection fraction (HFpEF). Today HFpEF, which is often the result of hypertension, obesity, and aging, is becoming more prevalent [16]. A systemic proinflammatory state that causes coronary microvascular endothelial inflammation has been proposed as one of the main mechanisms that drive HFpEF development [9]. Coronary microvascular endothelial inflammation is believed to disturb the nitric oxide balance, protein kinase G (PKG) activity in adjacent cardiomyocytes may drive sarcomeric alterations, and, together with enhanced interstitial fibrosis, they promote diastolic dysfunction [9]. For HFrEF, therapeutic options that include β -blockers, angiotensin-converting-enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs), which can slow down disease progression, are available; however, none of the current therapies have been shown to be successful in clinical trials with HFpEF. Together, this exemplifies that HF is not a single syndrome but a complex disorder, and we urgently need methods to distinguish the different HF modalities and underlying processes.

In addition to the clinical investigation, echocardiography is an important tool to diagnose HF, and it can be used to distinguish certain types of HF and to monitor disease progression [1,17]. However, it does not provide insight in the underlying molecular and cellular processes. Plasma biomarkers have the potential to provide information about specific processes (e.g. interstitial/replacement fibrosis, endothelial dysfunction, and pathological hypertrophy) that drive cardiac dysfunction and the transition from compensated to decompensated HF in the individual HF patient; they may also add prognostic value and help in guiding therapy.

Established heart failure biomarkers

Cardiac strain markers

Several biomarkers have been included in the guidelines for HF treatment of the European Society of Cardiology (ESC) and American Heart Association (AHA) [1,2].

The scientific evidence for the use of natriuretic peptide levels is overwhelming and their use in the clinic is widely established [18]. The two most important variants, atrial-type natriuretic peptide (ANP) and B-type natriuretic peptide (BNP), are mainly produced and secreted by the atria and ventricles, respectively [18]. Cardiac wall stress, generating mechanical strain in cardiomyocytes, enhances the production and secretion of these peptides [19–21]. ANP and BNP are synthesized as proANP and proBNP precursor proteins; upon secretion into the circulation, the N-terminal inactive domains (NT-proANP and NT-proBNP) are cleaved off, releasing the active ANP and BNP hormones [22,23]. ANP and BNP reduce peripheral vascular resistance and blood pressure by inducing a shift in fluid from the intravascular to the extravascular compartment, by promoting natriuresis, and by reducing the sympathetic tonus in peripheral vessels [18,24]. ANP and BNP are removed from the circulation by receptor-mediated internalization and metabolism and via proteolytic degradation by neprilysin (also termed neutral endopeptidase). Due to faster clearance of ANP by both pathways, the circulating half-life of ANP is only 3–5 min as compared to 23 min for BNP. Because of its very short half-life and its instability in plasma, ANP is not an attractive biomarker; thus either BNP or NTproBNP (half-life 60–120 min) are currently being used as biomarkers [23,25]. The stable mid-region of NT-proANP, MR-proANP, is also mentioned in the ESC guidelines for diagnostic and prognostic purposes, particularly in acute HF [1,26].

Plasma levels of natriuretic peptides are widely used in the diagnosis of patients who are suspected to have HF and are valuable in the evaluation of patients with both HFrEF and HFpEF [1,27]. Normal levels of natriuretic peptides largely exclude the presence of HF, and therefore levels are particularly useful to rule out HF, especially in the acute setting [1,27–30].

The levels of natriuretic peptides can be influenced by other syndromes and diseases, and kidney dysfunction is an important factor that may elevate natriuretic peptide levels [31]. In addition, obesity may be associated with lower natriuretic peptide concentrations and this may modestly reduce the diagnostic sensitivity in morbidly obese patients [32]. Importantly, with the positive results of clinical HF trials with entresto (LCZ-696) [33,34], the introduction of this drug in daily clinical HF practice will make the interpretation of BNP levels in such treated patients more difficult. Entresto is made up of the angiotensin-receptor blocker (ARB), valsartan, and the neprilysin inhibitor prodrug, sacubitril; the latter inhibits degradation of natriuretic peptides, thereby enhancing their beneficial effect during cardiac stress [35]. The concept that the lower the BNP levels in

chronic HF patients, the better the prognosis during treatment monitoring will no longer hold true in these patients. Because NT-proBNP and MR-proANP are not subject to breakdown by neprilysin, these biomarkers can still be used for patient monitoring in this setting [36].

Cardiac injury markers

Troponin I and T are another pair of proteins that are mentioned in the HF guidelines [1,2]. Troponins are released upon myocardial damage and elevated plasma levels of troponin point to acute coronary syndrome or pulmonary embolism as the cause of acute decompensation [1,37]. Like natriuretic peptides, the advantage of troponins is the cardiac origin of these proteins; although skeletal muscle also contains troponins, these isoforms are not detected by the cardiac specific isoform assays [38,39]. With the development of high sensitivity cardiac troponin (hsTn) tests, elevated levels of cardiac troponin can be measured in the absence of acute myocardial damage, in particular in patients with stable chronic HF [37]. It has been suggested that troponins are also released during chronic low-grade cardiac ischemia, necrosis, apoptosis, and autophagy [1,37]. Therefore, hsTn can be elevated because of ongoing myocardial damage, which is present in patients with non-acute chronic HF, in the absence of a clear episode of myocardial ischemia [1,37]. The example of troponin shows that, although a marker can be tissue specific, in this case, cardiac specific, it is not necessarily disease specific (e.g. elevated in both acute myocardial ischemia due to myocardial infarction and chronic low grade myocardial damage in HF). Because dead cardiac myocytes are not renewed but are replaced by fibrosis [11], it is tempting to suggest that cardiac troponins could be considered as plasma biomarkers of ongoing replacement fibrosis in HF (Figure 1).

The impasse of novel HF biomarkers

Extracellular matrix turnover and remodeling markers

Both natriuretic peptides and troponins show that different biomarkers provide different types of information. Therefore, a multi-marker approach has been suggested to combine the information provided by established and novel HF biomarkers to improve the current management and evaluation of HF patients. For this purpose, besides natriuretic peptides and troponins, the biomarkers, galectin-3 (Gal-3), and soluble

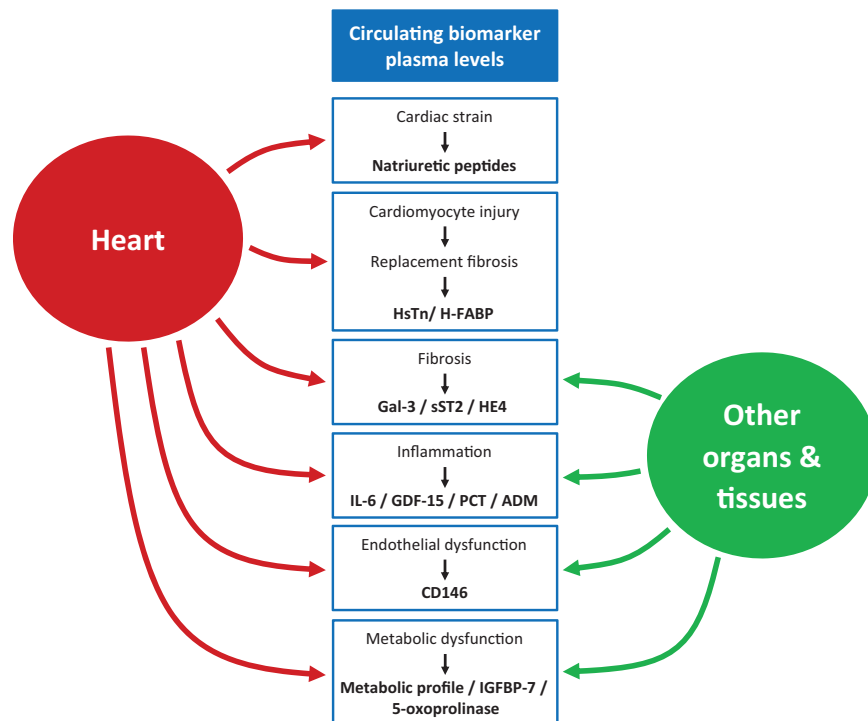


Figure 1. Novel heart failure biomarkers are not cardiac specific. A schematic depiction of the contribution of the heart and other organs and tissues to circulating plasma levels of several protein/peptide heart failure (HF) biomarkers. Only a selection of biomarkers is cardiac specific and many (novel) HF biomarkers are also produced in other organs and tissues. Within the boxes, the names of the biomarkers and associated processes are shown. Abbreviations are explained in the text.

suppression of tumorigenicity 2 (sST2), were included in the American College of Cardiology (ACC)/AHA HF guidelines as markers of myocardial fibrosis, with a class IIb recommendation, to be considered for additional risk stratification of HF patients [1,2]. Gal-3 and sST2 and their relation to HF have been extensively investigated and reviewed [6,7,40–42]. The inclusion of these novel biomarkers in official guidelines supports their possible additive value, but despite numerous years of intense investigations, the potential of these biomarkers remains vague.

Fibrosis marker Gal-3

Galectin-3 (Gal-3) is a marker of organ fibrosis, including cardiac fibrosis [7,43]. Plasma levels are increased in patients with HF and can have additional prognostic value to NT-proBNP levels [7,44]. Many clinical association studies have shown that plasma levels of Gal-3 are associated with cardiac function and LV-filling pressures [45,46]. Moreover, studies in animal models of HF revealed that Gal-3 was involved in cardiac remodeling, and both genetic disruption and pharmacological inhibition of Gal-3 resulted in reduced cardiac remodeling, including myocardial fibrosis [43,47–52]. However, because HF is a multi-organ syndrome, other organs could also contribute to increased Gal-3 levels in HF.

Gal-3 is expressed in multiple tissues and in different types of cells, including macrophages, eosinophils, neutrophils, and mast cells [47,53]. Gal-3 is also involved in renal fibrosis, as shown by several animal studies [51,54], and plasma levels of Gal-3 are increased in several other diseases, including chronic obstructive pulmonary disease (COPD), and several types of cancer [55–57]. Therefore, it is likely that the observed increases in plasma levels of Gal-3 in HF are associated with increased cardiac Gal-3 production, but also with production in other organs and/or tissues. In line with this, Gal-3 is associated with HF comorbidities, including obesity [58]. Unfortunately, the HF clinical association studies and animal studies that have been performed do not provide full clarity on this matter. In some clinical studies, Gal-3 plasma levels were not directly related to specific cardiac parameters of HF, including echocardiographic parameters [59]. Moreover, a study in which endomyocardial biopsies were taken from dilated and inflammatory cardiomyopathy patients revealed that Gal-3 levels in these biopsies did not reflect plasma Gal-3 levels [60]. Finally, in HF patients with elevated Gal-3 plasma levels prior to heart transplantation, the levels did not decline post-transplantation, which indicated that other non-cardiac sources were predominantly responsible for elevated Gal-3 plasma levels in these patients [61]. Altogether, Gal-3 is not a cardiac-specific

marker and it is unclear which organs and tissues contribute to the increased Gal-3 plasma levels, and to what extent, in HF. The use of Gal-3 as a biomarker for stratification of HF patients and as a marker of cardiac remodeling should therefore be interpreted in view of this possible multi-organ contribution.

Fibrosis marker sST2

Some of the issues discussed above also apply to sST2. Several clinical studies have shown that sST2 plasma levels are increased in patients with both acute and chronic HF and are predictive for HF outcome [62,63]. In both humans and mice, sST2 plasma levels are temporarily increased post-myocardial infarction, indicating that it could also act as a marker for myocardial injury [64]. ST2 has four isoforms, including sST2, ST2L, ST2V, and ST2LV; ST2L is the transmembrane isoform, and sST2 lacks transmembrane properties [41]. ST2L can interact with interleukin-33 (IL-33), and the ST2/IL33 interaction is involved in several diseases, including cardiovascular disease [41,42]. Triggered by cardiac strain or myocardial injury, cardiomyocytes and cardiac fibroblasts produce IL-33, which, by binding to ST2L, exerts cardioprotective effects by reducing cardiac hypertrophy and myocardial fibrosis [41,42]. sST2 is also produced by cardiomyocytes and cardiac fibroblasts, but it is associated with adverse cardiac remodeling via its competitive binding to IL-33, thereby limiting the protective effects of the ST2L/IL33 interaction [41,42,65]. Thus a relationship exists between sST2 and cardiac dysfunction [41,66]. A recent study showed that sST2 plasma levels normalized within 3 months post-implantation of a left ventricular assist device (LVAD) in end-stage HF patients [67]; this indicates that unloading the heart by LVAD placement lessens fibrosis. Because these are end-stage HF patients, many of whom will have multi-organ involvement, this finding may not be limited to the heart. In the ACC/AHA HF guidelines, sST2 has been included as a biomarker for myocardial fibrosis for further stratification of HF patients [1,2]. Like Gal-3, increased sST2 plasma levels are also present in other diseases, including gastric cancer, breast cancer, nephropathy and liver disease [68–71]. Thus, although sST2 is able to promote cardiac remodeling locally, plasma levels of sST2 may be influenced by production in other organs in HF patients; hence circulating levels do not necessarily mirror cardiac production and remodeling.

Fibrosis marker HE4

The marker human epididymis protein 4 (HE4) is a recently discovered novel HF biomarker. HE4 is also known as the whey acidic protein four-disulfide core

domain 2 (WFDC2 or WAP-4C). Though the exact function of HE4 is yet unknown, a role for HE4 in fibrosis formation has been suggested because it shows similarities to extracellular proteinase inhibitors [72,73]. In a mouse model of renal disease, reduced fibrosis was observed in mice treated with HE4-neutralizing antibodies [74]. In patients with both acute and chronic HF, HE4 levels were correlated with HF severity and could predict outcome in a multivariable model [75,76]. In both studies, HE4 levels in HF were correlated with Gal-3 and, therefore, probably with organ fibrosis. HE4, however, is not cardiac specific; its expression was first identified in the epididymis and later in many other tissues and organs [72,77,78]. Moreover, HE4 plasma levels are associated with several types of cancer [77–79], including ovarian cancer [80], and with chronic kidney disease (CKD) severity [81]. The association of HE4 levels with kidney function has also been replicated in cohorts comprised of acute and chronic HF patients [75,76]. It has been suggested that the elevated levels of HE4 in CKD patients may complicate its use in monitoring patients with epithelial ovarian cancer [82], and the same is probably true in the HF setting. These multi-disease effects on HE4 plasma levels will mean that HE4 will not be useful for HF diagnosis, but, as part of a multi-biomarker model, it may have potential in the stratification of HF patients. HE4 has been included in such a model as an instrument to identify populations with a distinct therapy response. Patients with acute HF were investigated for response to treatment with the selective A1 adenosine receptor antagonist, rolofylline; in this study, the authors assessed tools to distinguish responders from non-responders to therapy [83]. A multi-marker model, including HE4 plasma levels, tumor necrosis factor alpha receptor 1 (TNF-R 1 α), sST2 and total cholesterol, appeared to be superior to clinical characteristics, including age, sex, and cardiac function, to differentiate non-responders from responders. This study showed that multi-marker tools provide opportunities to improve clinical testing of novel drugs [83]. Moreover, this study is an example of how plasma biomarkers can be used in a multi-marker setting for stratification of HF patients.

Metabolic markers

Metabolic marker IGFBP-7

Insulin-like growth factor-binding protein 7 (IGFBP-7) can bind to insulin-like growth factor 1 (IGF-1) and, by regulating the activity of the growth hormone/insulin-like growth factor-1 (GH/IGF-1) system, it influences growth in various tissues. Its affinity for IGF-1 is

relatively low compared to other IGFBPs [84,85]. It has, however, strong affinity for insulin, thereby reducing the binding of insulin to its receptor [86]. Interestingly, IGFBP-7 was investigated in an HF mouse model in which IGFBP-7 expression and plasma levels were increased in relation to cardiac hypertrophy, which showed a link between IGFBP-7 and HF development [87]. IGFBP-7 levels were also elevated in serum of patients with both HF_{rEF} and HF_{pEF} [88–90], and levels in these patients were also associated with prognosis [88,89]. As a biomarker, IGFBP-7 may be interesting especially for the HF_{pEF} population [90]. First, IGFBP-7 has been associated with diastolic dysfunction, an important characteristic of HF_{pEF} patients [88–90]. Second, IGFBP-7 levels were associated with insulin resistance and metabolic syndrome risk [91], which were associated with HF_{pEF} development by causing chronic low-grade inflammation [9]. It has been suggested that, in a multi-marker approach, IGFBP-7 levels can be used to link abnormalities in cardiac function and morphology to disturbances in the metabolic status of patients [90]. Further investigations will be needed to establish this association with HF_{pEF}. Urinary IGFBP-7 levels are, together with tissue inhibitor of metalloproteinase 2 (TIMP-2), predictive for acute kidney injury in decompensated HF and post-coronary artery bypass surgery [92–95]. Thus, in addition to being a plasma biomarker, levels in other body fluids such as urine can provide diagnostic and/or prognostic information about patients. Again, IGFBP-7 serum levels have also been associated with several other diseases, amongst them endometriosis, soft tissue sarcoma, and COPD [96–98].

Cardiac injury markers

Cell death marker H-FABP

Heart fatty acid-binding protein (H-FABP), which is produced predominantly in the heart, shows similarities to troponins as a marker. In cardiomyocytes, H-FABP is involved in cardiac metabolism through supplying mitochondria with long-chain fatty acids [99]. H-FABP is released upon ischemic myocardial damage and has been shown to be a myocardial injury marker in mice and in humans, especially in the early hours after myocardial infarction [100–103]. Interestingly, the prognostic capacity of H-FABP appears to be more accurate than hsTn levels; moreover, this also applies to patients with suspected acute coronary syndrome but with negative troponin levels [99,104]. Also, non-acute HF patients show ongoing myocardial damage and therefore, like hsTn, H-FABP is increased in chronic HF patients and will be a potential biomarker of myocardial

damage [105,106]. It has been suggested that H-FABP is involved in a vicious cycle of deterioration in HF patients because extracellular H-FABP affects cardiac contraction by reducing intracellular Ca^{2+} , which leads to more damage and therefore more extracellular H-FABP [99]. Indeed, increased H-FABP levels were observed in HF patients with ongoing myocardial damage, and these levels were prognostic for HF outcome [105,106]. Importantly, myocyte H-FABP levels are also influenced by exercise, plasma lipid levels, and PPAR- α agonists; hence, its intracellular levels reflect metabolic capacity [107]. In accordance with this, *H-FABP*^{−/−} mice showed a reduced tolerance to physical activity and were rapidly exhausted by exercise [108]. In cardiac tissue, reduced fatty acid uptake was observed in these *H-FABP*^{−/−} mice [109]. Although speculative, this suggests that the H-FABP/troponin plasma ratio could provide information about cardiomyocyte metabolic function in HF patients; thus, plasma H-FABP may not be limited to being a marker of only myocardial damage.

Inflammation markers

Inflammation marker IL-6

Inflammation is an important process in HF, and substances related to inflammation, such as interleukin-6 (IL-6), could serve as HF biomarkers [5,110]. In the acute phase after myocardial infarction, IL-6 elevation is beneficial because it induces anti-apoptotic mechanisms in cardiomyocytes, and it is believed to limit infarct size [110]. However, IL-6 can also alter Ca^{2+} handling, and long-term IL-6 signaling is associated with depressed cardiomyocyte function, myocardial hypertrophy, and decreased contractility [110,111]. Limiting the long-term effects of IL-6 on the failing heart by blockade of the IL-6 receptor could therefore result in improved cardiac function, and the IL-6 receptor has been identified as an HF treatment target [112]. In an ischemia/reperfusion mouse model of HF, IL-6 receptor blockade resulted in neither reduced cardiac remodeling nor smaller infarct size; however, treatment was started during the acute phase, which could explain why no effects were observed [113]. Also, in humans, inhibition of IL-6 has been tested, but it was not able to improve coronary flow reserve in patients post-myocardial infarction [114]. Nevertheless, because IL-6 has been shown to be involved in HF development, and because levels of this inflammatory marker are increased in HF and are able to predict HF outcome in various types of HF [5,115–119], it could serve as an HF biomarker. The use of IL-6 in a multi-biomarker model has been suggested

[120], but circulating IL-6 levels are also affected by factors like stress, physical exercise, gender and age [119]. Moreover, circulating levels are also increased in non-HF patients; for example, elevated IL-6 plasma levels were predictive for post-operative complications in patients post-abdominal surgery [121], and IL-6 levels were associated with outcome in acute stroke patients [122]. Thus, in HF, IL-6 could be a marker of inflammation in a multi-marker model, but this should be complemented by other markers to provide specificity and exclude other causes of elevated IL-6 levels.

Inflammation marker GDF-15

Growth differentiation factor 15 (GDF-15) is another inflammatory protein associated with HF. GDF-15 is a member of the transforming growth factor-beta superfamily [123]. Several studies have shown the involvement of GDF-15 in cardiac remodeling. In mouse cardiomyocytes cultured *in vitro*, GDF-15 expression and secretion were readily upregulated by ischemia/reperfusion stress, which was suggestive of autocrine/paracrine functions [124]. Mice lacking GDF-15 were more prone to ischemia/reperfusion damage, which indicated that GDF-15 could have cardioprotective effects (in contrast to other markers like Gal-3 and sST2) [124]. In particular, GDF-15 deficient mice showed increased recruitment of polymorphonuclear leukocytes to the infarct zone and had a higher chance to develop myocardial rupture [125]. GDF-15 also appears to be involved in myocardial hypertrophy, most likely through SMAD protein activation [126]. In patient cohorts, it was shown that circulating levels of GDF-15 were independent risk predictors for cardiovascular outcome [127–129]. Circulating levels are also associated with other diseases, for example, pulmonary embolism [130], pulmonary arterial hypertension [131], pneumonia, renal disease, and sepsis [132]. Plasma levels of GDF-15 cannot be directly associated with myocardial inflammation, but in a multi-marker model GDF-15, could improve risk prediction as a marker of general inflammation [133].

Inflammation marker PCT

Procalcitonin (PCT) is an inflammatory marker that has been associated with HF and that is under clinical evaluation [134]. PCT, the prohormone of calcitonin, is secreted by different types of cells from numerous organs in response to proinflammatory stimulation. PCT levels are strongly elevated in bacterial infections and it is an early marker for systemic inflammation, infection, and sepsis; potentially it could be used to monitor patients and guide antibiotic therapy [135]. The half-life

of PCT is about 24 h, and the molecule is stable both *in vivo* and *in vitro* [136]. PCT was originally postulated to be a proxy for unrecognized infection in acute HF [135]. Based on the BACH (Biomarkers in Acute Heart Failure) trial, PCT was also included in the ESC-HF guidelines for the potential assessment of acute HF patients with suspected coexisting infection, particularly for the differential diagnosis of pneumonia and to guide antibiotic therapy [137]. Mollar et al. [138] showed that PCT concentrations were also raised in patients admitted with acute HF with no evidence of infection and that it was associated with renal dysfunction and surrogates of venous congestion and inflammation. PCT has been shown to have prognostic value in acute HF patients, but whether this relates to concomitant infection rather than systemic inflammation requires further investigation [134]. Currently, the IMPACT-EU study (clinicaltrials.gov; NCT02392689), a large, multicenter, randomized controlled trial, is underway to compare PCT-guided patient management with standard management in emergency department patients with acute dyspnea and/or acute HF [134]. This study should confirm whether PCT-guided antibiotic therapy will improve patient outcome by early identification of acute HF patients with elevated PCT.

Inflammation marker ADM

Another member of the calcitonin gene-related peptide (CGRP) superfamily and potential HF biomarker is adrenomedullin (ADM) [139]. ADM is a 52-amino acid multifunctional peptide that exhibits vasodilatory potential and increases renal blood flow, natriuresis, and diuresis. Also, anti-inflammatory, anti-apoptotic, and proliferative properties have been linked to ADM, and it therefore appears to exhibit protective functions under diverse pathological conditions [139]. ADM is produced as a precursor protein called preadrenomedullin in numerous tissues including adrenal glands, endothelium, vascular smooth muscles, renal parenchyma, and cardiomyocytes. This protein undergoes complex processing, first generating pro-ADM, which subsequently is cleaved into multiple peptides including mid-regional proADM (MR-proADM) and ADM; the latter can exist in both a bioactive amidated form (bio-ADM) and a glycosylated inactive form [140]. Whether MR-proADM has biological activity is unclear, but because it is more stable than ADM, it is the preferred biomarker. Like PCT, MR-proADM is strongly elevated in sepsis and could be used as a prognostic marker and to guide the diagnosis and treatment of sepsis [140]. MR-proADM lacks specificity for the diagnosis of HF, but the BACH study demonstrated that MR-proADM had superior accuracy for

predicting 90-day mortality compared with BNP in acute HF [141]. Recently, a sandwich immunoassay has been developed to measure bio-ADM in plasma. Like MR-proADM, bio-ADM levels in acute HF patients were predictive for 30-day outcomes in these emergency department patients [142]. MR-proADM was also predictive for cardiovascular events in the general population [143]. Adrenomedullin is a substrate of neprilysin and hence its levels may be affected by treatment with neprilysin inhibitors; it has been suggested that the positive effects of neprilysin inhibition by sacubitril may be due in part to the inhibition of adrenomedullin and other bioactive peptides [144]. Despite many studies, there is no evidence yet that MR-proADM or bio-ADM can be used in a biomarker-guided therapeutic strategy.

Endothelial dysfunction

Endothelial dysfunction marker CD146

Cardiovascular diseases, including HF, are also characterized by endothelial damage [145,146]. Therefore, increased levels of a marker of endothelial cell damage could be a marker of disease severity. Moreover, such a biomarker could provide additional information about endothelial status. Different etiologies of endothelial injury are thought to result in the expression of different endothelial markers [146]. A novel marker of endothelial damage is soluble CD146 (sCD146; CD146, cluster of differentiation 146), which is a part of the junction between endothelial cells and which is responsible for maintaining tissue architecture [147]. Mechanical disruption of endothelial junctions probably results in shedding of the long CD146 isoform (CD146-L) present on endothelial cells, which results in sCD146 that can be found in the circulation [146,148]. sCD146 promotes angiogenesis, but also seems to be a marker of endothelial damage, atherosclerosis, and plaque instability [149–152]. In patients with acutely decompensated HF, circulating sCD146 levels were increased and could aid in diagnosing acute HF in patients who were difficult to stratify based on NT-proBNP levels only (e.g. in patients with NT-proBNP levels that were not high enough to include, but also not low enough to exclude, HF) [153]. In animal models of cardiac pressure overload, LV *CD146* gene expression was increased and correlated with lung weight and therefore with lung congestion [153]. Also, in patients with pulmonary edema, the severity of the disease on chest radiography was associated with plasma levels of sCD146 [154]. Interestingly, in a human model of peripheral venous congestion applied to one of the upper extremities of patients with chronic HF, sCD146 plasma levels

increased whilst NT-proBNP remained stable [155]. It appears that circulating sCD146 levels can be related to peripheral vascular stretch, and moreover, that it is a marker of systemic congestion. Its plasma levels are also increased in liver cirrhosis, renal failure, atherosclerosis, and COPD [152,156–159]. Therefore, sCD146 seems to be a general marker of congestion and endothelial status in HF, but also in other diseases.

Looking beyond circulating proteins: microRNAs and metabolites as HF biomarkers

microRNAs

In addition to using circulating proteins as HF biomarkers, recently several other circulating substances have been marked as potential novel HF biomarkers, including circulating microRNAs (miRNAs). The functions of miRNAs in HF, their role in the circulation and their potential as biomarkers are still elusive [160]. MiRNAs, which are post-transcriptional regulators of gene expression, were originally identified as regulators of embryonic development, including cardiac development [160]. Only later, a link between activation of the fetal gene program, miRNAs, and HF development was suggested [160–162]. For some solitary miRNAs, a role in pathological cardiac remodeling in animal models was found [160,163–166]. Also, in humans, the relationship between miRNAs and cardiac remodeling has been investigated. For example, myocardial and circulating miRNA-21 were both associated with the degree of myocardial fibrosis [167]. Several other studies showed associations between circulating miRNAs, including miR-20a, miR208b, and miR-34a, and processes of cardiac remodeling, making them potentially interesting biomarkers [168,169]. The miRNAs, miR-22-3p, miR-148b-3p, and miR-409-3p, were also associated with HF [170,171]. Interestingly, in human HF, decreased levels of a cluster of circulating miRNAs were associated with acute HF and were inversely correlated with biomarkers associated with worse clinical outcome [172,173]. Also, lower miRNA levels were associated with worsening of renal function [174]. When this set of circulating miRNAs identified in human samples was investigated in several rodent HF models, the observations in humans could not be replicated [175]. However, closer examination revealed that these miRNAs in humans were downregulated, particularly in acute HF, and not, or to a much lesser extent, in chronic HF. Moreover, a clear association with decreased circulating miRNAs and hemodilution, as a result of fluid overload, was observed in decompensated acute HF patients; this could at least partially explain the lowered circulating

miRNA levels [176]. Also, comorbidities such as diabetes were present in the human HF cohort that were absent in the animal models. Therefore, in HF animal models, the cardiac phenotype was investigated without the influence of other HF comorbidities that may strongly affect miRNA levels. These results strongly hint that these miRNAs do not solely reflect cardiac function.

Metabolites

Metabolic dysfunction is prevalent in HF and subsequent changes in metabolite profiles could potentially be used as HF biomarkers [177]. In HF, both myocardial and systemic changes in glucose oxidation, catabolism, β -oxidation, and the urea cycle are responsible for observed alterations in metabolite levels [177]. Several studies have shown that a collection of metabolites can serve as diagnostic tools for HF [178–181]. However, changes in metabolite profiles seem not to be disease specific, because similar differences were observed in serum samples of patients with diseases such as non-Hodgkin lymphoma, congestive HF, and community-acquired pneumonia (CAP) [182]. In separate studies, the levels of the metabolite, trimethylamine N-oxide (TMAO), were shown to be associated with the outcome in both acute HF and CAP patients [183,184]. This is not surprising because systemic metabolic dysfunction is a general process that can be observed in other diseases. A recent study by van der Pol et al. identified the gene, *OPLAH*, which encodes 5-oxoprolinase (5-oxoprolinase, ATP-hydrolyzing), as a cardiac fetal-like gene that was suppressed in HF [185]. *OPLAH* functions to scavenge toxic 5-oxoprolin, and diminished levels of *OPLAH* in animal HF models resulted in elevated levels of 5-oxoprolin and associated oxidative stress in cardiac tissue. This could be reversed by cardiac-specific overexpression of *OPLAH*. Not only cardiac, but also plasma levels of 5-oxoprolin were elevated in animals. Importantly, plasma 5-oxoprolin levels were also elevated in acute HF patients, and patients with elevated levels showed a worse outcome. Although *OPLAH* is not exclusively expressed in the heart, cardiac levels are relatively high and hence 5-oxoprolin levels in the plasma may be predominantly from cardiac expression. This makes 5-oxoprolin a potentially interesting metabolite and biomarker that may be less affected by interference from non-cardiac sources as compared to other metabolites.

The promise and major hurdle of new biomarkers

As discussed above, plasma biomarkers have the potential to provide information about specific processes

(e.g. cardiac strain, interstitial/replacement fibrosis, endothelial dysfunction, and pathological hypertrophic processes) that drive cardiac dysfunction in the individual HF patient; they may provide added prognostic value and could be used to improve and guide therapy. However, one major pitfall in this line of reasoning is that, except for cardiac strain and cardiomyocyte-specific cell death, these cellular and molecular processes are general processes and hence hallmarks of pathophysiological processes in other organs and tissues. Because HF is a multi-system disease affecting many tissues and organs throughout the body and because it is strongly associated with comorbidities, it is likely that these stress-related processes are also induced in non-cardiac tissues in these patients. Therefore, circulating levels of these plasma biomarkers in HF may demonstrate not only cardiac production but also production in other stressed tissues. Because these biomarkers monitor not only cardiac stress but also stress in other organs and tissues, it is not surprising that they have a strong prognostic value. Thus, although these novel biomarkers can provide insights in specific pathological processes, the lack of cardiac and/or HF specificity, as depicted in Figure 1 and Table 1, appears to hamper their clinical use. We postulate that this is the main reason why only the cardiac-specific HF biomarkers, especially natriuretic peptides and troponins, have found their way to the clinic, whereas non-cardiac specific markers are still under evaluation. This emphasizes that we must look at a different aspect of these novel biomarkers in order to exploit their potential. This will require more in-depth research as discussed below.

Include preclinical studies in animals in the investigation of novel HF biomarkers

In a scientific statement from the AHA, criteria for the evaluation of novel biomarkers of cardiovascular risk have been proposed [186]. It is important to determine their clinical utility and, moreover, to determine whether the novel biomarker improves clinical outcomes in a cost-effective way. In a recent paper, Ahmad et al. stated that novel biomarkers should be approached in a more systematic manner with a focus on the clinical utility of the markers [187]. These important improvements in clinical biomarker research should be embraced.

We propose an additional pillar of HF biomarker research that has been largely neglected, namely, pre-clinical investigations (Figure 2). As described in this review, a major issue is that most novel biomarkers are not cardiac and/or HF specific but are also associated with diseases affecting other organs and tissues.

Table 1. Overview of selected (novel) heart failure biomarkers and associated conditions besides heart failure.

| Heart failure biomarker group | Biomarkers | Biomarker level also associated with: | References |
|---|---|--|-----------------------------|
| Biochemical strain | Natriuretic peptides (i.e. BNP, NT-proBNP) | Fluid overload Obesity (lowering of levels) Kidney dysfunction | [18,22–24,26,31,32,192] |
| Cardiomyocyte injury | hsTn H-FABP | Myocardial infarction Myocardial infarction | [37–39] [99–103,105,106] |
| Extracellular matrix turnover and remodeling | Gal-3 | Kidney fibrosis Kidney dysfunction COPD Breast cancer Gastric cancer Obesity | [7,43–58] |
| | sST2 | Breast cancer Gastric cancer Diabetic nephropathy Liver failure | [41,42,62–66,68–71] |
| | HE4 | Ovarian cancer Kidney fibrosis Kidney dysfunction Colorectal cancer | [72–82] |
| Inflammation | IL-6 | Infection Post-surgery Stroke | [110,111,115–119,121] |
| | GDF-15 | Pulmonary embolism Pulmonary arterial hypertension Pneumonia Renal disease Sepsis | [126–132] |
| | PCT | Bacterial infection Pneumonia Systemic inflammation Sepsis Kidney dysfunction Venous congestion | [134,135,137,138] |
| | ADM | Sepsis Diabetic retinopathy Pneumonia COPD | [139,141–143,193–195] |
| Metabolism | IGFBP-7 | Hepatocellular carcinoma Insulin resistance Metabolic syndrome Kidney injury Endometriosis Diabetic hemodialysis Soft tissue sarcoma COPD | [87,91–98] |
| Endothelial dysfunction | CD146 | Pulmonary edema Peripheral venous congestion Liver cirrhosis Kidney dysfunction Atherosclerosis COPD | [146,148–159] |

ADM: adrenomedullin; BNP: brain natriuretic peptide; CD146: cluster of differentiation 146; COPD: chronic obstructive pulmonary disease; Gal-3: galectin-3; GDF-15: growth differentiation factor 15; HE4: human epididymis protein 4; H-FABP: heart fatty acid-binding protein; hsTn: high sensitivity cardiac troponin; IGFBP-7: insulin-like growth factor-binding protein 7; IL-6: interleukin 6; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; PCT: procalcitonin; sST2: soluble suppression of tumorigenicity 2.

Currently, plasma levels of novel biomarkers are investigated in human clinical cohorts, providing at best associations, whilst plasma biomarkers are rarely investigated in HF animal models (preclinical studies), which could provide more causal insights. A simple PubMed search showed about ten times more published HF biomarker studies in patient cohorts as compared to preclinical HF biomarker studies. In contrast, investigations of cardiac remodeling processes such as cardiac hypertrophy and fibrosis are much more equally distributed between preclinical and clinical studies.

Decreasing the gap between preclinical and clinical HF biomarker studies could provide more mechanistic insights required for proving causality (Figure 2). Preclinical animal studies could also provide us with accurate information regarding the exact tissue and cell sources that contribute to the HF biomarker plasma levels. Moreover, animal studies are well suited to investigate the effects of comorbidities on the plasma levels of biomarkers and to investigate time-related changes both in plasma and in other tissues (Figure 2). In clinical studies, we will at best be able to perform this in

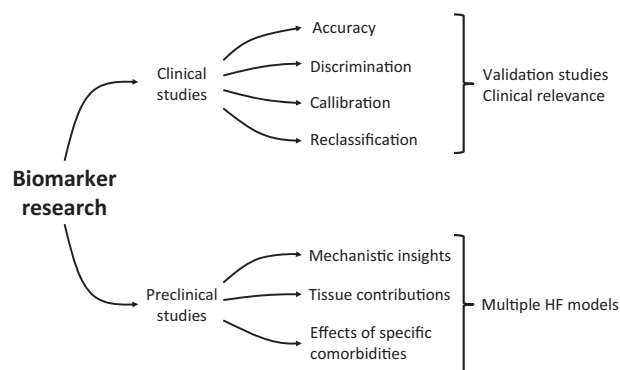


Figure 2. Two pillars of HF biomarker research. HF plasma biomarkers are currently predominantly investigated in clinical cohorts. Despite these investigations, progression in the clinical use of HF biomarkers is limited. Systematic improvements in clinical HF biomarker research have therefore been included to generate the required information [186,187]. We now propose an additional pillar of HF biomarker research, namely, the preclinical pillar, to provide additional information from studies in animals that should enhance our understanding, and together should pave the way to finally exploit these novel biomarkers. As in clinical studies, this will require systematic approaches and reports as indicated.

end-stage patients postmortem, but this will not provide information about the dynamics during HF development. Therefore, we suggest expanding translational animal experiments in which novel biomarkers can be studied at multiple levels. In line with clinical studies, these preclinical studies should be performed in a systematic manner and reported following guidelines such as the ARRIVE guidelines for animal studies [188]. It will also be crucial to invest in appropriate reagents to study biomarkers in animal models. So far, this has been a major limitation in animal studies, and even established HF biomarkers such as NT-proBNP and NT-proANP are seldom measured in mouse or rat studies because of the lack of good and affordable reagents (e.g. ELISA kits). Obviously, the small plasma volumes also make it challenging to measure these biomarkers in small animals. We believe that the current HF biomarker impasse can be broken by investing in preclinical studies to improve our understanding of these biomarkers, which finally could result in exploiting their full clinical potential.

Discussion

Established HF plasma biomarkers have proven their utility in the evaluation of HF patients, and novel HF biomarkers could further improve stratification of these patients. In the past decades, many novel HF biomarkers have been discovered and investigated in clinical trials. Despite these major efforts, only two novel

biomarkers, Gal-3 and sST2, have been included in the ACC/AHA HF guidelines, but also their clinical value is still uncertain. Although these biomarkers can show specific molecular and cellular processes (e.g. fibrosis, hypertrophy), they lack cardiac and/or HF specificity. In [Figure 1](#), a schematic depiction of the cardiac and non-cardiac specificity of HF plasma biomarkers is shown. This helps to explain why the investigated novel HF biomarkers have not yet been accepted into clinical use. Therefore, as depicted in [Figure 2](#), we suggest including more in-depth preclinical investigations in animal models to gain insight into the relationship between plasma biomarker levels and the processes of cardiac remodeling, and into the potential contribution of other affected organs and tissues. Eventually, this should result in multi-biomarker models. To increase the predictive value of multi-marker panels requires a comprehensive evaluation of a broad set of biomarkers that represent the many pathophysiological pathways involved in HF, as described here. Serial evaluation of multi-marker panels is needed to maximize their prognostic utility [189]. These models could be used both to determine the right therapy regime and to guide therapy. The idea of a multi-biomarker model is not new, but to date, no real advances have been made in developing these types of models. This is most likely because of our lack of understanding of the contributions of other tissues to biomarker levels, and preclinical studies will therefore be indispensable.

We suggest that analyzing non-cardiac specific HF biomarkers in a cardiac-specific way could be another way forward. Visualizing the local cardiac presence of these proteins and substances, for instance by using specific tracers in cardiac imaging, could provide direct information about the ongoing cardiac remodeling processes. Gal-3 could, for example, serve as a marker of myocardial fibrosis. This approach sounds futuristic, but for Gal-3, these types of tracers already exist [190,191]. Further research is needed to fully investigate this potential path to the utilization of non-cardiac specific biomarkers in a cardiac-specific manner.

In conclusion, most novel HF biomarkers provide evidence of specific molecular and cellular processes, but in a non-cardiac specific fashion. Therefore, it is still unclear whether altered plasma biomarker levels represent solely cardiac production and can be directly associated with the degree of cardiac remodeling. Clinical association studies will not provide sufficient information to solve these issues, because cardiac samples are often not available and full body biomarker profiling will not be realistic or may be impossible. As shown in [Figure 2](#), we therefore propose that comprehensive

biomarker plasma and tissue profiling in preclinical HF models, in addition to biomarker plasma profiling in clinical cohorts, is necessary to fully reveal the potential of these HF biomarkers.

Disclosure statement

All authors work for the University Medical Center Groningen (UMCG), Groningen, the Netherlands. The UMCG, which employs Dr de Boer has received research grants and/or fees from AstraZeneca, Abbott, Bristol-Myers Squibb, Novartis, Roche, Trevena, and ThermoFisher GmbH. Dr de Boer is a minority shareholder of scPharmaceuticals, Inc. Dr de Boer received personal fees from MadalMed Inc, Novartis, and Servier. Dr Silljé received research grants from AstraZeneca.

Funding

This work was supported by the Netherlands Heart Foundation [CVON DOSIS, grant 2014–40, CVON SHE-PREDICTS-HF, grant 2017–21, and CVON RED-CVD, grant 2017–11], and the Innovational Research Incentives Scheme program of the Netherlands Organization for Scientific Research (NWO VIDI, grant 917.13.350).

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